3083

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Mountz, et al.	§	**ART UNIT: 1647**
	§	
FILED: May 15, 1998	§	
	§	
SERIAL NO.: 09/079,834	§	**EXAMINER:**
	§	**Spector, Lorraine**
FOR: Fas Ligand Expressing	§	
Antigen Presenting Cells for	§	
ToleranceInduction	§	**DOCKET: D6005**

#29
M.Q-J
2/27/03

Assistant Commissioner of Patents
Box AF
Washington, D.C. 20231

ATTENTION: Board of Patent Appeals and Interferences

APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on December 31, 2002. The fees required under 37 C.F.R. §1.17(f) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is the University of Alabama at Birmingham Research Foundation.

II. STATUS OF THE CLAIMS

Originally, claims 1-17 were filed with this application. Claims 10-15 were withdrawn from consideration. Claims 2, 7 and 17 were canceled, and claims 1, and 16 have been amended. The pending claims 1, 3-6, 8, 9 and 16 are being appealed, of which claims 1 and 16 are independent claims.

III. STATUS OF AMENDMENTS

Claims 1 and 16 were amended in the Response to Office Action filed December 27, 2000. No claim amendments were made in response to the Final Office Action mailed September 3, 2002. All pending claims are shown in the Appendix.

IV. STATEMENT OF RELATED APPEALS AND INTERFERENCES

To Applicant's knowledge, there are no pending related appeals or interferences that will directly affect or be directly affected by the present appeal.

V. SUMMARY OF THE INVENTION

The present invention is drawn to a method of inducing systemic tolerance to a viral or alloantigen using antigen presenting cells engineered to express Fas ligand and the antigen of interest. These antigen presenting cells would induce apoptosis of Fas-positive T cells directed towards said antigen through the Fas ligand-Fas antigen interaction. Subsequently, systemic tolerance to said antigen is induced (Specification, page 9, line 3-page 10, line 5).

The present invention is also drawn to a method of using antigen presenting cells engineered to express Fas ligand to reduce graft rejection. Antigen presenting cells from a graft are engineered to express high level of Fas ligand. These antigen presenting cells would eliminate T cells reactive to the antigens of the graft as

described above. As a result, immune-privileged sites are created in which the graft is not rejected due to T cell tolerance. (Specification, page 24, line 19-page 25, line 10).

VI. ISSUES

35 U.S.C. §112

Whether claims 1, 3-6, 8, 9 and 16 are enabled under 35 U.S.C. §112, first paragraph.

VII. GROUPING OF CLAIMS

The rejected claims do not stand or fall together. Applicants consider claims 1, 3-6, 8, 9 and 16 encompass two embodiments of the present invention. Claims 1, 3-6 and 8-9 are drawn to a method of inducing systemic tolerance to a viral antigen, an autoantigen or an alloantigen using Fas ligand-expressing antigen presenting cells. In another embodiment, claim 16 is drawn to a

method of creating immune-privileged sites so as to decrease transplant rejection.

VIII. ARGUMENTS

The Rejection Under 35 U.S.C. §112

In the Final Office Action mailed September 3, 2002, the Examiner maintained the rejection of claims 1, 3-6, 8, 9 and 16 under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The present invention discloses a strategy in which introduction of antigen presenting cells (APCs) engineered to express high levels of Fas ligand together with a specific antigen could induce specific, systemic tolerance to the antigen. A series of experiments were performed to examine tolerance induction *in vivo* by these Fas ligand-expressing antigen presenting cells (Examples 17, 18, 20, 21 and Figures 7, 8, 10B and 11). It was shown that antigen presenting cells, which expressed Fas ligand and processed adenovirus antigens, can directly induce apoptosis of Fas-positive T cells. Pretreatment of

recipient mice with the adenovirus-transfected Fas ligand-expressing antigen presenting cells resulted in induction of T cell tolerance to the adenovirus. Induction of T cell tolerance to adenovirus required production of Fas ligand by the antigen presenting cells and did not occur with adenovirus-transfected, control antigen presenting cells. T cell tolerance also required expression of Fas by the T cells of recipient mice, as Fas-deficient lpr/lpr mice could not be tolerized. This is because T cell tolerance is a result of eliminating activated T cells by apoptosis which is induced upon binding the Fas antigens on the T cells to the Fas ligands expressed on the antigen presenting cells. The T cell tolerance was antigen-specific as there was normal T-cell response to murine cytomegalovirus (MCMV) in tolerized mice.

In a Declaration filed June 20, 2002, Applicants further submited data showing T cell tolerance induction by Fas ligand-expressing antigen presenting cells in murine models of Sjögren syndrome-like disease and arthritis. Sjögren syndrome is a chronic inflammatory disease characterized by infiltration of the exocrine glands with mononuclear cells and T cells. Induction of T cell tolerance resulted in dramatic amelioration of these diseases in the infected animals. Hence, Applicants submit that ample data have

been provided to show T cell tolerance induction by Fas ligand-expressing antigen presenting cells in not one but multiple disease models well-recognized in the art. In view of the generalized application of the present invention in multiple disease models, Applicants submit that one of ordinary skill in the art would have sufficient support to apply the claimed method to successfully induce systemic immune tolerance in a human.

In an attempt to show a potential problem in applying the instant invention to human, the Examiner made reference to the death of a patient in a gene therapy trial in the Final Office Action mailed March 23, 2001. The patient "died following an acute respiratory system collapse and subsequent multi-organ failure, apparently brought on by a massive immune system response". Applicants submit, however, the present invention is different and distinct from the above-referenced gene therapy trial and the purported problem is irrelevant to the claimed invention.

The present invention is designed to down-regulate immune responses by the expression and function of Fas ligand. In normal situations, naïve T cells become activated after interacting with antigen presenting cells that process and present antigens to the

T cells. The activated T cells are then capable of mediating a number of immune functions. These activated T cells also express Fas antigens on their surface. In the present invention, however, these activated T cells would be eliminated by apoptosis which is induced upon binding the Fas antigens on the T cells to the Fas ligands expressed on the antigen presenting cells. Consequently, T cell tolerance is induced and the individual would have significantly reduced immune responses towards the antigens presented by the Fas ligand-expressing antigen presenting cells.

Hence, it is not likely that the present invention would cause immune system over-reaction and death in a patient as suggested by the Examiner. Significant numbers of activated T cells that may mediate adverse immune responses would be eliminated by the Fas ligand-expressing antigen presenting cells as described above. This is supported by the results from the animal studies wherein dramatic amelioration of disease processes was observed. Therefore, the potential problem of immune system over-reaction or adverse effects in the settings of gene therapy trials (such as the one cited by the Examiner) would not be a problem in the instant invention

because the present invention is designed to eliminate reactive T cells that mediate these responses.

In order to practice the instant invention, one of ordinary skill in the art only need to generate by routine and standard molecular biology techniques engineered antigen presenting cells that express an antigen of interest and Fas ligand. After being introduced to an individual by standard procedure, these antigen presenting cells would engage and present antigens to naïve T cells just like normal unmodified antigen presenting cells. Consequently, activated T cells that are reactive to the antigens presented by these modified antigen presenting cells would be eliminated by apoptosis as described above. Hence, Applicants submit that no undue experimentation is required in the making, administering and using of the engineered antigen presenting cells as claimed herein.

Based on the data disclosed herein, Applicants submit that the detailed description of *in vivo* effects of the Fas ligand-expressing antigen presenting cells disclosed in the specification has provided sufficient enablement for using said antigen presenting cells to induce T cell tolerance in human. The scope of the claims is commensurate with the enablement provided. Accordingly, Applicants respectfully

request that the rejection of claims 1, 3-6, 8, 9 and 16 under 35 U.S.C. §112, first paragraph, be withdrawn.

Respectfully submitted,

Date: Feb 19, 2003

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com

CLAIMS ON APPEAL

1. (twice amended) A method of inducing systemic tolerance to an antigen in an individual in need of such treatment, comprising the step of:

administering to said individual antigen presenting cells which (1) express high level of Fas ligand resulted from co-infection with AdLoxPFasL and AxCANCre adenoviruses, (2) do not express Fas and (3) express said antigen, wherein said antigen presenting cells induce apoptosis of Fas-positive T-cells directed towards said antigen resulting in said induction of systemic tolerance to said antigen.

3. The method of claim 1, wherein said antigen is selected from the group consisting of the adenovirus antigen, a viral antigen, an adeno-associated viral antigen, an autoantigen, and an alloantigen.

4. The method of claim 1, wherein said individual has an autoimmune disease.

5. The method of claim 4, wherein said autoimmune disease is selected from the group consisting of diabetes, multiple sclerosis, rheumatoid arthritis, thyroiditis, Grave's disease, systemic lupus erythematosus.

6. The method of claim 1, wherein said individual has had an organ transplant.

8. The method of claim 1, further comprising the step of delivering to said antigen presenting cells a gene to inhibit apoptosis.

9. The method of claim 8, wherein said gene to inhibit apoptosis is crmA.

16. (twice amended) A method of creating immune-privileged sites in an individual so as to decrease rejection of a graft, comprising the steps of:

extracting antigen presenting cells from donor organ tissue;

introducing Fas ligand into said antigen presenting cells by co-infection with AdLoxPFasL and AxCANCre adenoviruses to produce Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft;

introducing said Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft to said individual prior to and during said grafting procedure; wherein said Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft create said immune-privileged site at the site of said grafting procedure to prevent rejection of said graft in said individual.